Some Diagnostic and Therapeutic Techniques in Cystic Fibrosis of the Pancreas

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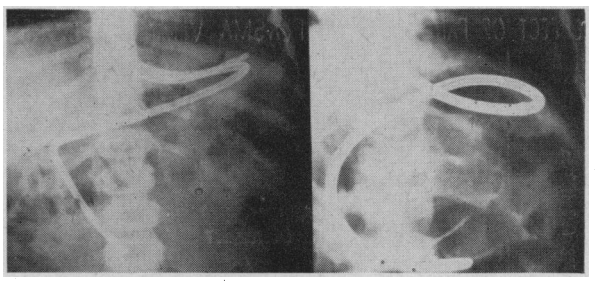
THE frequency of cystic fibrosis of the pancreas was appreciated only as recently as 1938.[2] The incidence has been estimated to be 1.7 per 1000 live births in New York City.[3] With the advent of penicillin some improvement in the prognosis has occurred.[11] Differentiation between cystic fibrosis of the pancreas and the various other entities of the celiac syndrome is often difficult, while the confidence resulting from a definite diagnosis favors adequate pursuance of the appropriate therapies.

The typical case of the fibrocystic disease is in an infant or child with history of chronic cough; soft, foul, bulky stools; retarded weight gain and growth, enlarged abdomen, poor musculature, and perhaps x-ray evidence of pulmonary inflammation and fibrosis. Microscopic examination of the stool for excess fat by sudan stain is a technique available to any office and is of great usefulness as a rough measure to aid in recognition of the celiac syndrome.[4]

In diagnosis of cystic fibrosis of the pancreas most reliance has been placed on the absence of trypsin from the duodenal fluid. In adults the most adequate technique of duodenal drainage has utilized the bi-lumen, gastro-duodenal tube. The gastric lumen permits withdrawal of the gastric fluid so that it does not contaminate the duodenal specimen. The need for such a technique, but the lack of successful application of it to infants, has been indicated by Andersen.[1]

In the present studies an attempt has been made to fill this need. Before a small double-lumen tube was devised, double drainage was accomplished by means of two separate tubes, one through each nostril (or one or both through the mouth in infants without teeth). Two tubes in place are shown in Figure 1A. This procedure was used in 30 tests and seemed to accomplish the objective of minimizing contamination of the duodenal sample by gastric contents. The duodenal tube was of 12 (French) diameter and had a gold tip. A 10 F or 12 F tube was used for the gastric drainage. The difficulties seemed to be due to the tendency of the two tubes to adhere so that introduction of the gastric tube after placement of the duodenal was somewhat more uncomfortable to the child, sometimes resulting in regurgitation of the duodenal tube into the stomach. Any separate adjustment of the tubes was difficult but the technique was usable and is desirable if a small bi-lumen tube is not available.

Figure 1B shows a bi-lumen tube, use of which has been apparently successful and thoroughly convenient in 31 attempts in patients ranging down to newborn size. This tubing also has 12 F outside diameter and is 120 cm. long.* It has two equal lumina, semicircular in cross section side by side. A gold tip of the same diameter (4 mm.) 15 mm. length, and 2.7 gm. weight is attached to the bottom.† Holes for the duodenal juice are immediately above this.



A B

Figure 1.—(A) X-ray showing two separate single-lumen tubes in place for separate drainage of gastric and duodenal fluids in a three-year-old child. (B) X-ray showing a bilumen tube in a 10-month-old infant. The duodenal tubes in the two films are of the same outside diameter (12 French).

Seventeen cm. higher, in the other lumen, are holes for gastric juice. This lumen is blocked below the gastric holes by a metal plug. Stubs of 15 gauge needles are tied into the upper end, through which aspiration is made alternately with syringes.

Entry of the tube into the duodenum is facilitated by placing the child on the right side. Directed by the weight of the tip, the lower perforations reach the pool of fluid in the pyloric corner of the stomach, as indicated by a steady drip or easy aspiration of fluid. Water is injected to maintain such a pool until the appearance of yellow juice usually heralds the passage of the tube into the duodenum. When clear, alkaline, yellow fluid is obtained from the lower lumen, while acid, turbid, white fluid comes simultaneously from the gastric, there can be little doubt that the tube is properly placed even without fluoroscopic verification, although the latter has always been used in the present study. In some cases, particularly in pancreatic deficiency, no duodenal fluid was obtained at first, and only at fluoroscopy was the tube discovered to be in the duodenum.

A good quantitative trypsin method is essential. In several debilitated infants without specific pancreatic deficiency the trypsin concentration was so low as to be undetectable by inexact office procedures, but high enough to rule out a typical case of cystic fibrosis of the pancreas.

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* The rubber tubing was made through the courtesy of Mr. Emil Davidson, Clay-Adams Company, New York City.

† The gold tip was made through the courtesy of Dr. W. A. Elsasser and Dr. W. L. Wylie, University of California College of Dentistry.

Values of 58 x 10^{-4} units of trypsin, 15 x 10^{-4} units lipase and 83 x 10^{-3} units amylase per cc. were obtained in the control child of whom the vitamin A curves are shown in Figure 2. This was a well-nourished two-year-old boy with occasional rectal prolapse. The infant in Figure 2 with pancreatic deficiency had zero values for trypsin, lipase and amylase. This infant had meconium ileus in the newborn period. She later developed a chronic cough. The duodenal drainage was done at the age of 8 weeks. (At this age a normal infant also shows no amylase.) The child representing celiac disease was 27 months old and had enzyme values of 21 x 10^{-4} U trypsin, 19 x 10^{-4} U lipase and 59 x 10^{-3} U amylase.

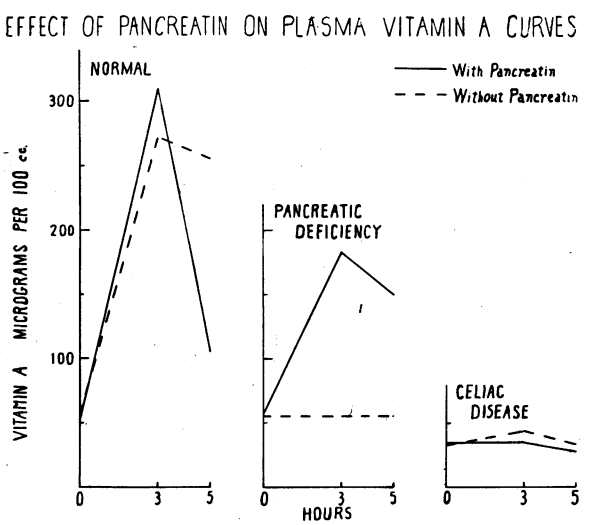

Figure 2

The rise in plasma vitamin A concentration which normally follows an oral test dose of vitamin A ester in fish oil does not appear in the celiac syndrome. Administration of pancreatin tends to correct the curve in pancreatic deficiency.[10] Curves from an infant with cystic fibrosis of the pancreas are presented in Figure 2. In this illustration the lack of effect of pancreatin on the normal curve of a normal child and on the flat curve of a child with celiac disease is also shown. These curves approximate the average obtained in 17 cases of cystic fibrosis of the pancreas, 10 cases of non-pancreatic celiac syndrome, and 12 controls. Use of this effect as a diagnostic measure has seemed a helpful adjunct to duodenal drainage. Its reliability is being further investigated.

Meanwhile the therapeutic implications of the effect deserve emphasis. The rise in vitamin A serves as an index of the effectiveness of pancreatin in restoring not only the digestion of vitamin A ester, but probably also of other foodstuffs. Inability to digest vitamin A ester may be circumvented by use of vitamin A alcohol.[10] Similarly, amino acids may be used to replace protein.[14] Prolonged use of an artificially hydrolysed, complete diet would, however, be difficult. The present data contribute to the assurance that relatively normal digestion can be achieved by the simple and practical expedient of adequate pancreatin therapy.[7] Corresponding data concerning the effect of pancreatin in protein digestion as indicated by blood amino acid concentrations has been presented by other workers.[16]

Dosage of 0.3 to 1.5 gm. of enteric-coated pancreatin granules following each meal has been used for routine therapy in the present series. 0.15 gm. pancreatin for each kg. body weight and 7000 units kg. vitamin A as halibut liver oil have been the test doses for the vitamin A curves. The tests were started before breakfast or the early morning formula and other vitamin concentrates were withheld.

Vitamin A curves with pancreatin in patients with pancreatic deficiency are also useful for comparison of the effectiveness of different pancreatin preparations and dosages.

Vitamin A has been determined by the Carr-Price reaction,[12] § pending acquisition of equipment for use of a capillary-blood method.[8]

In view of the fact that vitamin A levels of the plasma are depressed in both infection and impaired intestinal processes, determination of fasting vitamin A is of unique value in the follow-up of these cases.[13] In view of the possible effect of vitamin A deficiency to aggravate the pulmonary disease it seems advisable to keep the fasting vitamin A level within or above the normal range. This can be accomplished by high vitamin A dosage, pancreatin and antibiotics. We are using 15,000 to 50,000 USP units of vitamin A daily in most patients. As other indications of the status of the patients, the weight gain, leukocyte count, the penicillin sensitivity of the pulmonary flora and the interval history concerning cough, fever, and stools are also significant.

PENICILLIN AEROSOL

The terminal development in cystic fibrosis of the pancreas has been pulmonary infection. Benefit from use of penicillin has been dramatic. It seems obvious, however, that the best possible nutritional state, as maintained by vitamin A, pancreatin, etc., would

The studies here reported were done by the method of Anson, in which tyrosine from a hemoglobin substrate is determined with use of a photoelectric colorimeter.[5] The hemoglobin was prepared by dialysis of human over-age bank-blood. The more recent method using sulfanilamide azoprotein would probably also be satisfactory.[9] Amylase was determined by the volumetric hypoiodite method of Willstatter.[11] Lipase was determined by titration of the fatty acids liberated from 1.2 millimols benzyl butyrate in a bile-glycerol mixture.[6] One lipase unit liberates one milli-equivalent of fatty acid per minute. Units are otherwise as defined in the references except that all digestions were done at 37.5°C. These three determinations could be completed within an hour. The tubes of juice were kept in an ice bath during collection and frozen if not immediately analyzed.‡

‡ I am indebted to Dr. I. L. Chaikoff and Dr. S. Chernick, Division of Physiology, University of California, for suggestions concerning the enzyme methods.

§ The method was standardized by use of the USP Vitamin A Reference Standard distributed by the Board of Trustees of the United States Pharmacopoeial Convention, 4738 Kingsessing Avenue, Philadelphia 43, Pa.

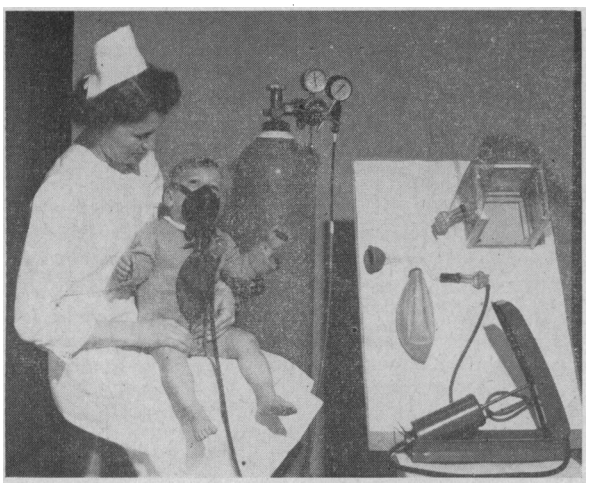

Figure 3.—Various equipment for penicillin aerosol administration.

be prerequisite to maximal success in penicillin therapy. Low fat diet and postural drainage are probably also of benefit.

The danger in patients receiving penicillin is the appearance of penicillin-resistant organisms. Such an outcome is believed to be facilitated by inadequate penicillin therapy. In our present program the periods (usually one to two weeks) of penicillin (25,000 to 50,000 units four times daily) alternate with periods without penicillin of a duration depending on the time of return of increased cough. Sulfonamides are usually used in prophylactic oral dosage during the periods when penicillin is not given. On the hospital ward, penicillin is given intramuscularly along with the aerosol inhalation. The program of use of aerosol alone represents a compromise with expediency which is practical in the home.

Some of the various arrangements for penicillin inhalation are illustrated in Figure 3. The oronasal B. L. B. mask is shown on the child.* The assemblies on the other side of the picture are alternative equipment. The box is for small infants. Some patients use oxygen tanks at home. Others have inexpensive automobile foot-pumps as illustrated. The foot-pump is especially satisfactory in case of a ten-year-old boy who coordinates his inhalations with strokes of the pump, and holds the nebulizer directly in his mouth. When a foot-pump is used it is advisable to insert a wad of gauze somewhere in the air line to catch any trace of oil, and the gauze should be changed from time to time. Difficulty has been encountered of some nebulizers being ineffectively constructed. Sometimes plugging of the small jet also occurs. Nebulizers must be tested occasionally by being held up to the light during use, for observation of the mist.

Twenty cases of cystic fibrosis of the pancreas have been studied at the University of California Hospital in the past year. Repeated weight records of 14 of the patients on essentially the regime recommended previously in this presentation, are at hand. Nine of the 14 have gained weight at a rate greater than the normal average for the age. Four others have also gained weight, but at a rate somewhat slower than the average. One, who was first seen after advanced pulmonary changes, lost weight over a six month period, was found to have a penicillin-resistant organism, responded poorly to streptomycin, and died.

* Size 4 B has been used, but is no longer available. We plan to use size 5 C instead. Mask and nebulizer assemblies are available through the University of California Pharmacy.

SUMMARY

Construction and use of a double-lumen gastroduodenal tube for duodenal drainage in infants is described.

The effect of pancreatin to raise the plasma vitamin A tolerance curve in pancreatic deficiency is illustrated and its therapeutic significance emphasized.

Equipment for administration of penicillin aerosol is illustrated and discussed.

REFERENCES

1. Andersen, D. H.: The relationship of celiac disease, starch intolerance and steatorrhea, J. Ped., 30:564 (May), 1947.

2. Andersen, D. H.: Cystic fibrosis of the pancreas and its relation to celiac disease, Am. J. Dis. Child., 56:344 (August), 1938.

3. Andersen, D. H.: Cystic fibrosis of the pancreas, Brenneman's Practice of Pediatrics, I Ch. 29 A, F. W. Prior, Hagerstown, Md.

4. Andersen, D. H.: Determination of fat in feces: reliability of two chemical methods and of microscopic estimate, Am. J. Dis. Child., 69:141 (March), 1945.

5. Anson, M. L.: The estimation of pepsin, trypsin, papain and cathepsin with hemoglobin, J. Gen. Physiol., 22:79 (Sept.), 1938.

6. Balls, A. K., and Matlack, M. B.: The enzymic hydrolysis of benzyl stearate and benzyl butyrate, J. Biol. Chem., 125:539 (Oct.), 1938.

7. Beazell, J. M., Schmidt, C. R., and Ivy, A. C.: Diagnosis and treatment of achylia pancreatica, J.A.M.A., 116:2735 (June), 1941.

8. Bessey, O. A., and Lowry, O. H., Brock, M. J., and Lopez, J. A.: The determination of vitamin A and carotene in small quantities of blood serum, J. Biol. Chem., 166:177 (Nov.), 1946.

9. Charney, J., and Tomarelli, R. M.: A colorimetric method for the determination of the proteolytic activity of duodenal juice, J. Biol. Chem., 171:501 (Dec.), 1947.

10. Clausen, S. W., McCoord, A. B., and Goff, B. L.: A comparison of absorption of ester and alcohol vitamin A by human subjects, Fed. Proc., 5:129 (Feb.), 1946.

11. diSant'Agnese, P. E. A., and Andersen, D. H.: Chemotherapy in infections of the respiratory tract associated with cystic fibrosis of the pancreas; chemotherapy with penicillin and drugs of the sulfonamide group with special reference to penicillin aerosol, A. J. Dis. Child., 72:17 (July), 1946.

12. Kaser, M., and Stekol, J. A.: A critical study of the Carr-Price reaction for the determination of β-carotene and vitamin A in biological materials, J. Lab. Clin. Med., 28:904 (April), 1943.

13. McKhann, C. F.: The malnourished child, Clinics, 5:601 (Oct.), 1946.

14. Shohl, A. T., May, C. D., and Shwachman, H.: Studies of nitrogen and fat metabolism in infants and children with pancreatic fibrosis, J. Pediat., 23:267 (Sept.), 1943.

15. Schmidt, C. R., Greengard, H., and Ivy, A. C.: A comparison of methods for the quantitative estimation of diastase in duodenal fluids, Am. J. Dig. Dis., 1:618 (Nov.), 1934.

16. West, C. D., Wilson, J. L., and Eyles, R.: Blood amino nitrogen levels, A. J. Dis. Child, 72:251 (Sept.), 1946.

QUESTIONS AND ANSWERS

Question: Has any child with cystic fibrosis and lung changes ever reached puberty?

DR. GIBBS: The oldest child that we have is ten years old, and judging by the way he is doing now, he should reach puberty. The oldest among Andersen's reported cases was 14½ years. I believe that there is a degree of mildness in cases, and we are at present investigating the probability that some fibrocystics may be mild enough so that they have survived into adulthood, although so far this has not been demonstrated.

Question: You stated the incidence of pancreatic fibrosis as being 1.7 per thousand. That seems a surprisingly high incidence to most of us. The question is: Does that not mean that a great many cases are being missed?

DR. GIBBS: That is Dorothy Andersen's figure for New York City; we will have to take her word for it. This estimate seems more and more reasonable in view of the increasing number of cases that are being proven here—cases that in the past would have been fatal with some indefinite diagnosis.

MODERATOR: What is the adequate dosage of pancreatin?

DR. GIBBS: We are feeling our way in that; it depends on the type of pancreatin that is used. The dosage that I am using therapeutically ranges from 0.3 to 1.5 grams of enteric-coated pancreatin granules after each meal. As judged by the effect on the vitamin A absorption curve, plain pancreatin should be given in twice the dosage.

Question: Have you employed liver extract and vitamin B parenterally to raise vitamin A absorption? (2) Have you performed the amino acid absorption curve as a substitute for duodenal assay as in New York City?

DR. GIBBS: We use liver and vitamin B in celiac disease, and it seems very effective in certain cases. I doubt whether the amino acid absorption test is as reliable as duodenal assay. I have not used the amino acid test myself, but I mentioned the work of West and Wilson at Ann Arbor. They have, incidentally, obtained for amino acids essentially the same difference in curves with and without pancreatin, as I showed here for vitamin A. They determined the amino acids liberated from casein or gelatin.

Question: Does B_1 and liver injection still play an important part in the treatment of fibrocystic disease of pancreas?

DR. GIBBS: That is an idea that should be played with. True celiac disease may be a sort of vitamin deficiency, something related to the vitamin B group, and it may possibly be precipitated by various types of intestinal disturbances including cystic fibrosis of the pancreas. I am waiting for a case of fibrocystic disease in which the nutrition and diarrhea do not respond to pancreatin, and will respond to vitamin B and liver, but have not found one yet.